REMARKS

Claims 1 to 7, 9 to 10 and 18 to 27 are pending in the application. Claim 6 has been canceled without prejudice or disclaimer. Claims 1 to 5, 7, 9 to 10 and 18 to 27 have been amended, and Claims 28 to 33 have been added. No new matter has been added by the amendments or the new claims. The Commissioner is hereby authorized to charge deposit account 02-1818 for any fees which are due and owing.

Claims 1 to 7, 9 to 10 and 18 to 27 were objected to for informalities that have been corrected. Applicants respectfully submit that the objections have been overcome.

Claims 4, 5 and 7 were rejected under 35 U.S.C. §112, second paragraph for indefiniteness.

In particular Claim 4 was rejected for referring to "a sequence of bases of IS*S1* and a functional equivalent thereof". As described in the reference cited in the Specification at page 5, line 17, bacterial insertion sequences (IS) undergo replicative transposition in the chromosome of bacteria to allow integration of plasmids between duplicated insertion sequences. Insertion sequences, however, vary among different strains of bacteria in terms of their number of base pairs, host, positions and frequency on the chromosome but perform a common function. For example, there are three families of IS elements including IS*S1* and iso-IS*S1* elements defined in lactococci; both undergo replicative transposition in the chromosome of lactococci to allow integration of plasmids between duplicated insertion sequences. See *J. Bacteriology* 178, page 931 (1996). Therefore, one of skill in the art would recognize a functional equivalent of a sequence of bases of IS*S1* as in Claim 4.

Claim 5 was rejected for lack of clarity. In response, Applicants have amended Claim 5 to clarify that the bacterial chromosome comprises addition of DNA at at least one site chosen from the group consisting of a site which disrupts expression of a chorismate mutase chain A gene, a site which disrupts expression of the downstream gene ORF 394 and a site which disrupts expression of an oxidoreductase gene. Accordingly, Applicants respectfully submit that the subject matter of Claim 5 is now clear and that the rejection has been overcome.

Claim 7 was rejected for referring to "a deletion of at least part of ORF 1560", wherein the phrase "at least part of" is allegedly undefined. Applicants have described in the

Specification at, for example, page 9, lines 4-16, at least two 500 bp fragments within the 1560 bp ORF that are deleted by homologous recombination. Therefore, one of skill in the art would understand a deletion of 500 base pairs within an open reading frame of 1560 base pairs (ORF 1560) to be at least part of ORF 1560. Applicants, therefore respectfully submit that the phrase "at least part of" is sufficiently defined and that the rejection should be withdrawn.

Claims 1 to 4, 6 to 7, 9 to 10 and 18 to 27 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. Applicants respectfully submit that the Specification provides the skilled person complete guidance to obtain an *S. thermophilus* bacterial strain having the desired trait of being resistant to bacteriophage attack. As acknowledged in the Office Action at page 5, the Specification is "enabling for a modified *S. thermophilus* having a modification of bacterial chromosome in ORF90 due to an inserional mutation which disrupts the expression of the chorimate mutase chain A gene or in ORF269 due to an inserional mutation resulting in disruption of expression of the encoded oxidoreductase gene or a deletion in the prophage genome of ϕSfi21 in ORF1560 which disrupts the expression of the prophage, and starter culture and milk products thereof." Applicants respectfully submit that the modifications as recited in the claims are modifications that include addition of DNA at a specific site or deletion of DNA at a specific site and are not just "any" modifications of the ϕSfi21 prophage or the bacterial chromosome. By way of example, the Specification teaches disrupting expression of the prophage at ORF1560 of the ϕSfi21 prophage. The Specification also teaches disrupting expression of the chorismate mutase chain A gene at ORF90 and/or ORF394. The Specification sets forth at page 14, lines 30-33 that this disruption of expression may prevent the interaction between phage structural proteins and bacterial structures required for DNA injection into the host.

Methods for disrupting the expression of open reading frames, either in a plasmid, a (pro)phage or genome, are well known to the skilled person. In particular, the Specification at, for example, page 4 et seq., discloses a number of well-known techniques, such as site-directed integration, transposition, assay for selection of phage-resistant mutants, etc., to disrupt host factors required at various steps of the bacteriophage life cycle such as DNA injection. To do this, one must disrupt the expression of proteins involved in the infection process through the addition or deletion of DNA at a specific site. Such methods may comprise the generation of a plasmid allowing integration of DNA in a specific site(s) of the gene to be "knocked out" by

single or double cross-over events. Such a deletion may be carried out according to the deletions performed in ORF1560 as sufficiently described at, for example, page 9, lines 6-16 of the Specification. The Specification further sets forth at, for example, page 14, lines 9-11 that the mutant strain, Sfi1c16Δ1560, does not release detectable infectious particles upon challenge. Moreover, plaque assays demonstrated additional suppression of phage infectivity of said bacterial strain (Table 2, of the present specification). See Specification at, for example, page 13, line 39 through page 14, line 24. Therefore, Applicants respectfully submit that the Specification provides sufficient guidance to one of skill in the art to practice the claimed invention.

Claims 1, 3 to 4, 9 to 10, 19, 21, 23 and 26 were rejected under 35 U.S.C. §102(b) as being anticipated by a publication to Sturino M. et al. entitled "Construction of Bacteriophage-Resistant Strains of *Streptococcus themophilus* by pGh9::ISS1 insertional mutagenesis" published in Journal of Dairy Science 81(Supp. 1): 7 in 1998 ("*Sturino*"). Claims 1 to 2, 6, 9 and 18 to 20 were rejected under 35 U.S.C. §102(b) as being anticipated by a publication to Foley et al. entitled "A Short Non-Coding Viral DNA Element Showing Characteristics of a Replication Origin Confers Bacteriophage Resistance to *Streptococcus themophilus*" published in Virology 250(2): 377-87 on October 25, 1998 ("*Foley*").

Sturino fails to teach or suggest a *Streptococcus thermophilus* bacterium which is resistant to attack by at least one bacteriophage and which comprises a modification of an ϕSfi21 prophage by deletion of sufficient DNA to disrupt expression of the prophage in the bacterium. As acknowledged in the Office Action at page 9, *Sturino* does not teach or suggest "the deletion of non-coding viral DNA element confers bacteriophage resistance to *S. thermophilus*." The bacterial strain of the claimed invention is rendered resistant to phage replication within the bacterial cell by mutation which has occurred at specific sites by deleting sufficient DNA such as at least part of ORF1560 of the ϕSfi21 prophage genome such that phage replication within the bacterial cell is prevented. Accordingly, replication of phages within the cell that are normally present in the form of prophages ready to enter their lytic cycle is prevented.

In contrast, *Sturino* relates to the generation of bacteriophage insensitive mutants of *S. thermophilus* through plasmid-mediated mutagenesis. *Sturino*, lines 5-8. In particular, a jud29 phage element is added to the bacterium at non-specific sites to induce phage resistance, but does

not teach or suggest preventing propagation or replication of phages within the cell by, for example, inactivating the prophage through DNA deletion as in the claimed invention.

Foley also does not disclose preventing replication and propagation of phage within the cell by deletion of DNA in the ϕSfi21 prophage genome sufficient to prevent expression of the prophage. *Foley* describes a non-coding DNA fragment present in the genome of the ϕSfi21 phage thought to act as an origin for DNA replication of the phage. The non-coding DNA fragment is not deleted from the DNA replication module of ϕSfi21 as suggested in the Office Action, page 9, but is cloned into a shuttle vector to be added to the Sfi1 strain of *S. thermophilus* to transform the bacterium. Therefore, *Foley* does not teach or suggest a *S. thermophilus* bacterial strain which has been mutated by deletion of sufficient DNA in a ϕSfi21 prophage genome to disrupt expression of the prophage such that phage propagation within the bacterium is substantially prevented as in the claimed invention. Accordingly, Applicants respectfully submit the rejection has been overcome and should be withdrawn.

Claims 22, 24, 25 and 27 were rejected under 35 U.S.C. §103(a) as being unpatentable over *Sturino* in view of *Foley*. Applicants respectfully submit that the rejection has been overcome and should be withdrawn.

Sturino alone, or in combination with *Foley*, does not teach or suggest a starter culture or a milk product having an *S. thermophilus* bacterial strain which has been mutated in the ϕSfi21 prophage genome by deletion of at least part of ORF1560 as in Claims 24 and 27. As acknowledged in the Office Action at page 9, *Sturino* does not teach or suggest the deletion of non-coding viral DNA element confers bacteriophage resistance to *S. thermophilus*. To attempt to cure this deficiency of *Sturino*, the Office Action combines *Foley* with *Sturino*. Even if such a combination is proper, *Foley* lacks the same features as *Sturino*. In particular, the non-coding DNA fragment described in *Foley* is not deleted from the ϕSfi21 prophage, but rather is cloned into a shuttle vector to be added to the bacterial genome. Therefore, *Sturino* alone, or in combination with, *Foley*, does not teach or suggest each and every element of the claimed invention, and one of skill in the art would not be motivated by *Foley* to modify *Sturino* to arrive at the claimed invention.

For the foregoing reasons, Applicants respectfully request reconsideration of their patent application and earnestly solicit an early allowance of same.

Respectfully submitted,

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Dated: May 15, 2006